193976

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NEW ZEALAND

PATENTS ACT 1953

PROVISIONAL SPECIFICATION

"Improvements in or relating to methods of making intra-vaginal devices and/or intra-vaginal devices"

WE, AHI OPERATIONS LIMITED, a company duly incorporated under the laws of New Zealand of 640 Great South Road, Manakau City, Auckland, New Zealand DO HEREBY DECLARE this invention to be described in the following statement:

NEW ZEALAND

PATENTS ACT, 1953

No.: 193976

Date: 9 June 1980

COMPLETE SPECIFICATION

"Improvements in or relating to methods of making intra-vaginal devices and/or intra-vaginal devices"

I/We, AHI OPERATIONS LIMITED a company duly incorporated under the laws of New Zealand of 640 Great South Road, Manukau City, Auckland, New Zealand

hereby declare the invention for which I/ we pray that a patent may be granted to ~~me~~/us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

This invention relates to methods of making intra-vaginal devices and/or intra-vaginal devices.

It is an object of the present invention to provide methods of making intra-vaginal devices and/or intra-vaginal devices which will at least provide the public with a useful choice.

Accordingly in one aspect the invention consists in an intra-vaginal device for the sustained release of an active ingredient when inserted into an animal, including:

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a) a flexible, non-toxic skeleton forming a resilient supporting portion having at least three lobes with inner ends joined to each other at a common centre, and radiating from the common centre to give a ~~generally~~ substantially star shaped configuration, and

b) a polymeric coating moulded over at least the free ends of the lobes to form a skin thereupon, and having the active ingredient incorporated therein, the active ingredient and coating being chosen to permit a controlled rate of release of the active ingredient when the device is in contact with the bodily fluids of the animal.

In a further aspect the invention consists in an intra-vaginal device for the sustained release of an active substance into the vagina of an animal when inserted therein, including a resilient non toxic supporting skeleton and a polymeric coating having the active ingredient incorporated therein moulded over the skeleton to form an active skin thereupon, the active ingredient and the skin affording a sustained release of active ingredient during contact with the body fluids of the animal, and the skeleton including means for increasing the surface area of the active skin exposed to the body fluids comprising at least three lobes radiating in a plan from a central body portion, each of which lobes is perforated with a network of holes over which the skin is moulded to provide an undulated skin surface over the skeleton and increase the skin surface area exposed to body fluids.

In a still further aspect the invention consists in an

the Authorities, such as the Animal Remedies Board to have animals injected with drugs. The question of possible residues of substances after injection is an increasing concern to such Authorities. This concern may be amplified by restrictions imposed overseas by the U.S. Federal Drug Administration and its E.E.C. equivalents. An outstanding example of this is the banning of stilboestrol in the U.S. despite the fact that carcass residues have never been demonstrated.

The present invention in the preferred form proposes the incorporation of an active ingredient in the skin of a two part device having a body and the skin and for example the active ingredient may be progesterone or an oestrogen or a mineral trace element such as selenium cobalt and copper and boron.

The present invention will now be described with reference to the accompanying drawings in which:

Figure 1 is a spread out view of a device according to the invention having one lobe of the device coated with a skin, the other two lobes representing the skeleton,

Figure 2 is a cross section on the line AA figure 1,

Figure 3 is a particular sketch of the device including a withdrawal arrangement, and

Figure 4 is a perspective sketch showing a different type of withdrawal arrangement.

Referring to the drawings, in figure 1 a body 1 is moulded with a plurality of arms or lobes for example between 3 and 7 from a suitable plastics material such as polypropylene polyethylene or ethylene vinyl acetate which are non-toxic

intra-vaginal device for the sustained release of a active ingredient into the vagina of an animal comprising:

a) a flexible, non toxic skeleton comprising a central body portion and a plurality of lobes radiating therefrom; and

b) a polymeric coating moulded over at least three ends of the lobes to form a skin thereupon, and having the active ingredient incorporated therein at least adjacent the surface thereof.

In a still further aspect the invention consists in a method of manufacturing an intra-vaginal device for the sustained release of an active substance into the vagina of an animal, the method comprising forming from a flexible, non toxic material a skeleton comprising a central body portion and a plurality of lobes radiating therefrom, moulding over at least the free ends of the lobes a polymeric coating to form a skin thereupon and incorporating the active ingredient into the coating at least adjacent the surface thereof.

In many situations the physiology of pharmacology of an animal process is well enough understood that it can be manipulated by active ingredients such as hormones, drugs and minerals, but the exploitation is limited by the lack of practical methods of administering the active ingredients.

For example,oestrus synchronisation by progestogens in sheep and cattle has been known for more than 30 years but nether injection or feeding sheep or cows is a practical procedure especially under pastural conditions.

As well as the practical difficulties involved in the administration of drugs, the question of residues is becoming increasingly important. In many cases it is unacceptable to

and flexible materials. Each of the lobes is perforated with a network of holes 2 as shown in figure 2 so that a drug carrying or active ingredient carrying polymer coating 3 may be moulded around at least the free ends of the lobes of the body 1 so that the active ingredient is provided in the skin and at least adjacent the surface thereof while the lobes form the skeleton of the device. Because the active ingredient is in the skin, it is available on the surface thereof for its pharmaceutical property. At the other end of each of the lobes of the body 1 is a hole through which may be threaded a withdrawing ligament 5 which may be moulded as a separate unit with a "T" shaped head on each length of the ligament the other end of each length being joined to a connecting point of loop 6 so that tension may be applied to the loop 6 to withdraw the device from the animal. Alternatively ligament 5 may be moulded in one piece with body 1 to substantially eliminate post moulding assembly costs. Another possible rearrangement of the withdrawing filament or ligament is shown in figure 4 where the members 10 carrying the T ends on two of the lobes pass through a ring 11 on the third lobe and are connected to a single filament 12.

We have however found as a result of an extensive programme of application and removal of the devices, that the simplest and most effective method of effecting removal is to have a filament 15 (figure 1)(which may be mono filament or multi-filament cord) looped through a hole 16 in one lobe of the device to provide withdrawal action by pulling on that one lobe only. When this one lobe is pulled, the other two lobes will fold over and trail behind as the device is

withdrawn from the animal. This has been proven to give most reliable withdrawal with the least possible risk of discomfort or damage to the animal.

After moulding of the body or skeleton 1 in the suitable non-toxic and flexible material, the skeleton 1 is transferred to another mould in which the polymer substance 3 is moulded. Such a substance is, for example, a modern rapid curing two component silicone rubber which is moulded around each of the lobes 1. Such a rubber is available from the Dow Corning Corporation and has curing times which vary from one month at ambient temperature to five seconds at 200°C. By using an appropriate temperature e.g. one approaching 200°C, this silicone rubber can be cured very rapidly. During moulding of silicone rubber the two components of the silicone rubber are introduced into the moulding machine just prior to injection. The active ingredient whether it be a testosterone, progesterone, oestrogen or other substance is premixed with one of the silicone rubber components or alternatively may be dosed automatically as the two silicone rubber components are fed into the mould of the moulding machine.

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The foregoing describes an intra-vaginal device of particular configuration but other physical configurations are possible with the device which is characterised by being simply and cheaply produced by normal moulding such as injection moulding in two stages, firstly by moulding a skeleton or carrier and secondly by coating that carrier as required with a suitable substance e.g. a polymer which acts as a drug release polymer coating. We have found that a two part high speed curing silicone rubber is a feasible substance in this regard.

As may be seen from the drawings the surfaces of the skin are extended by indentations or undulations so that the surface area exposed to body fluids is increased. Such undulations or indentations may have a smooth profile so they do not unnecessarily collect or harbour bacteria or collections of bodily substances.

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A central orifice 7 may be provided in the carrier moulding to allow for draining or flow of bodily fluids and/or withdrawal of the device by means of a suitably attached cord should this be preferred to the arrangements above described.

The insertion of the device may be effected by folding the lobes into a closed position after which the natural elasticity of the lobes will cause these to open against the internal surfaces of the vagina or other bodily orifice to retain the device in said position securely and without discomfort to the animal.

While the incorporation of drugs in a polymer device and its removal at the end of a treatment period does not completely eliminate the problems of residues, it is more acceptable to many approving authorities and they will consider a procedure such as induction of lactation, by the administration of oestrogens via a polymer device where injections of oestrogens are completely unacceptable.

In addition, sustained release of drugs has many other advantages. The amount of drug (or other substances) required to achieve a desired effect is often substantially reduced compared with injection or ingestion. Where substances are ingested the uptake by the gut and the metabolism of the

entro-hepatic circulation offer substantial barriers to the effectiveness of materials reaching the target site.

Also, the passage of material through the gut is essentially a limiting factor to the effective time of an oral dose of a substance. With both injections and oral dosing, the material is usually in a soluble form and reaches high concentrations both at the site of administration and in the blood. This can cause complications both through local toxicity and in other parts of the body. As the clearance of a material is proportional to its concentration this means that usually, a large amount of injected material is wasted when sufficient is injected to act over a 24 hour period because of the high clearance at the time of such blood levels. With sustained release, the blood level of material can be maintained at much closer to the effective level. This frequently means that as well as reducing or avoiding toxicity problems, the amount of administered material is substantially reduced often by a factor of 100 or more.

The release of drugs from polymers has a wide variety of applications to animal production in New Zealand and in other countries. Many drug carrying devices have been devised and their descriptions published.

These have all suffered from limitations either in their effectiveness in use, damage or discomfort to the animal and/or the cost effectiveness and/or high labour cost of production.

Devices have been described for assistance in synchronisation of oestrus in sheep and cattle, for induced lactation in cattle, for induced calving etc.

Testosterone treatment of cows induces them to perform male mounting behaviour, so assisting in the detection of animals which are ready for mating.

It is possible to stimulate lactation by the administration of growth hormones; and many other possibilities exist for the application to animals of various minerals and drugs for a number of reasons.

For example one or more mineral trace elements in addition to or instead of a hormonal or oestrogenic or anthelmintic ingredients may be incorporated in the skin during manufacture thereof. In such cases the skin may be of ethylene vinyl acetate or other polymer and may be integral with the body or skeleton of the device.

The body or skeleton acts as a mechanical framework or support and the skin is an outer covering of sufficient thickness so that in use the skin erodes away freeing the active ingredient over a satisfactory period of time, the active ingredient being leached out by action of the animal's body fluids.

WHAT WE CLAIM IS:

1. An intravaginal device for the sustained release of an active ingredient when inserted into an animal, including:

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a) a flexible non toxic skeleton forming a resilient supporting portion having at least three lobes with inner ends joined to each other at a common centre, and radiating from the common centre to give a ~~generally~~ substantially star shaped configuration, and

b) a polymeric coating moulded over at least the free ends of the lobes to form a skin thereupon, and having the active ingredient incorporated therein, the active ingredient and coating being chosen to permit a controlled rate of release of the active ingredient when the device is in contact with the bodily fluids of the animal.

2. A device as claimed in claim 1, wherein each of the lobes of the supporting portion is perforated with a network of holes over which the skin is moulded.

3. A device as claimed in claim 1 or claim 2 wherein the coating is moulded over at least the free ends of the lobes by injecting a two component liquid Silicone rubber over the supporting portion in a mould, and curing

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the rubber.

4. An intravaginal device for the sustained release of an active substance into the vagina of an animal when inserted therein, including a flexible, resilient non-toxic supporting skeleton and a polymeric coating having the active ingredient incorporated therein moulded over the skeleton to form an active skin thereupon, the active ingredient and the skin affording a sustained release of the active ingredient during contact with the body fluids of the animal and the said skeleton including means for increasing the surface area of the active skin exposed to the body fluids comprising at least three lobes radiating in a plan from a central body portion, each of which lobes is perforated with a network of holes over which the skin is moulded to provide an undulated skin surface over the skeleton and increase the skin surface area exposed to body fluids.

5. A intravaginal device as claimed in claim 4 wherein the skin is moulded over the skeleton by injecting a two-component liquid silicone rubber containing the active ingredient over the skeleton in a mould, and curing the rubber.

6. An intravaginal device for the sustained release of an active ingredient into the vagina of

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an animal comprising:

a) a flexible, non-toxic skeleton comprising a central ~~cnetral~~ body portion and a plurality of lobes radiating therefrom; and

b) a polymeric coating moulded over at least the free ends of the lobes to form a skin thereupon, and having the active ingredient incorporated therein at least adjacent the surface thereof.

7. An intravaginal device ~~as~~ as claimed in claim 6 wherein each of the lobes of the skeleton is perforated with a network of holes over which the skin is moulded.

8. An intravaginal device as claimed in claim 6 or claim 7 wherein the skeleton includes at least three intercontrolled lobes foldable to lie close to each other for insertion or removal.

9. An intravaginal device as claimed in claim 8 wherein the lobes are intercontrolled by a withdrawing ligament associated with apertures in the free end of the lobes.

10. An intravaginal device as claimed in ~~carim~~ claim 6 or claim 7 having at least three lobes, and further including means for withdrawing the device from the vagina comprising a filament attached to the free end of one of the lobes so that the remaining lobes flex and fold over within the vagina and trail behind as the

filament is pulled and the device withdrawn.

11. An intravaginal device as claimed in any one of claims 6 to 10 wherein the device is formed as a two part article by first forming the skeleton and then ~~forming~~ moulding the skin on the skeleton, the skin having the active ingredient incorporated therein during moulding of the skin onto the skeleton.

12. An intravaginal device as claimed in claim 6 wherein the skin is formed integrally with the skeleton.

13. An intravaginal device as claimed in claim 11 wherein said skeleton is moulded of a thermoplastics material such as polypropylene or polyethylene.

14. An intravaginal device as claimed in claim 11 or claim 13 wherein said skin is formed from a high-speed curing silicone rubber.

15. An intravaginal device as claimed in claim 14 wherein the high-speed curing silicone rubber is a two component silicone rubber.

16. An intravaginal device as claimed in claim 15 wherein the active ingredient is premixed with one or both of the silicone rubber components before mixing of the two components in a moulding machine just prior to injection.

17. An intravaginal device as claimed in claim 15 or claim 16 wherein the active ingredient is dosed

automatically as the silicone rubber components are fed into moulding parts of a moulding machine.

18. An intravaginal device as claimed in any one of claims 11 to 17 wherein the skin is formed from ethylene vinyl acetate or other polymer substance.

19. An intravaginal device as claimed in any one of claims 11 to 18 wherein the device has depressions or undulations in the surface thereof to increase the surface area of the skin.

20. An intravaginal device as claimed in any one of claims 1 to 18 wherein active ingredient is one or more of progesterone, oestrogen, testosterone, selenium, cobalt, copper, boron, or anthelmintics.

21. An intravaginal device substantially as hereinbefore described with reference to the accompanying drawings.

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~~22. An intravaginal device as claimed in any one of the preceding claims for insertion into a cow or sheep.~~

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~~23~~ 22. A method of manufacturing an intravaginal device for the sustained released of an active substance into the vagina of an animal, the method comprising forming from a flexible, non-toxic material a skeleton comprising a central body portion and a plurality of lobes radiating therefrom, moulding over at least the free ends of the lobes a polymeric coating to form a

skin thereupon and incorporating the active ingredient into the coating at least adjacent the surface thereof.

~~24~~ 23. A method as claimed in claim ~~23~~ 22 wherein the ~~actico~~ active ingredient is incorporated into the coating during the moulding of the coating upon the skeleton.

~~25~~ 24. A method as claimed in claim ~~24~~ 23 wherein the coating is formed from a high speed curing silicone rubber.

~~26~~ 25. A method as claimed in claim ~~25~~ 24 wherein the silicone rubber is a two component silicone rubber, the two components being mixed immediately prior to moulding the coating upon the skeleton.

~~27~~ 26. A method as claimed in claim ~~26~~ 25 wherein the active ingredient is pre-mixed with one or both of the two components before mixing of the two components in the moulding machine and just prior to injection moulding of the coating upon the skeleton.

~~28~~ 27. A method as claimed in claim ~~26~~ 25 or claim 27 wherein the active ingredient is dosed automatically as the silicon rubber components are fed into moulding machine.

~~29~~ 28. A method as claimed in any one of claims ~~23~~ 22 to 28 wherein the lobes are perforated with a network of holes over which the skin is moulded.

~~30~~ 29. A method as claimed in any one of claims ~~23~~ 22

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to ~~29~~ 28 wherein the skeleton is made of polyethylene or ethylene vinyl acetate.

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~~31~~ 30. A method of manufacturing an intravaginal device substantially as hereinbefore described.

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DATED THIS 27th DAY OF February 1984

A. J. PARK & SON

PER V. P. Hume

AGENTS FOR THE APPLICANT

Fig.3.

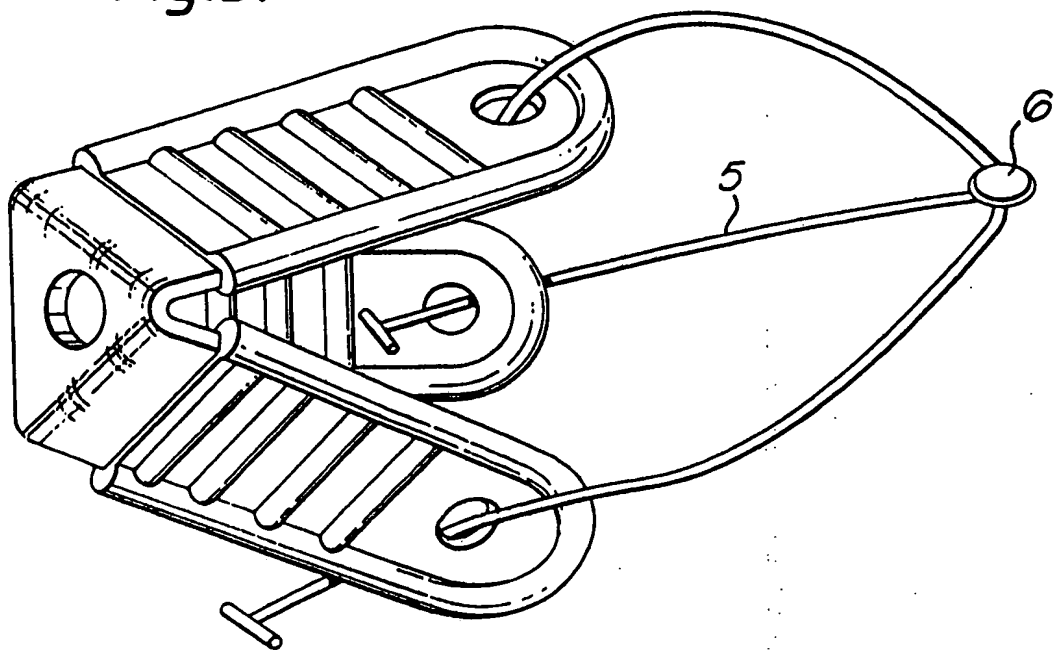
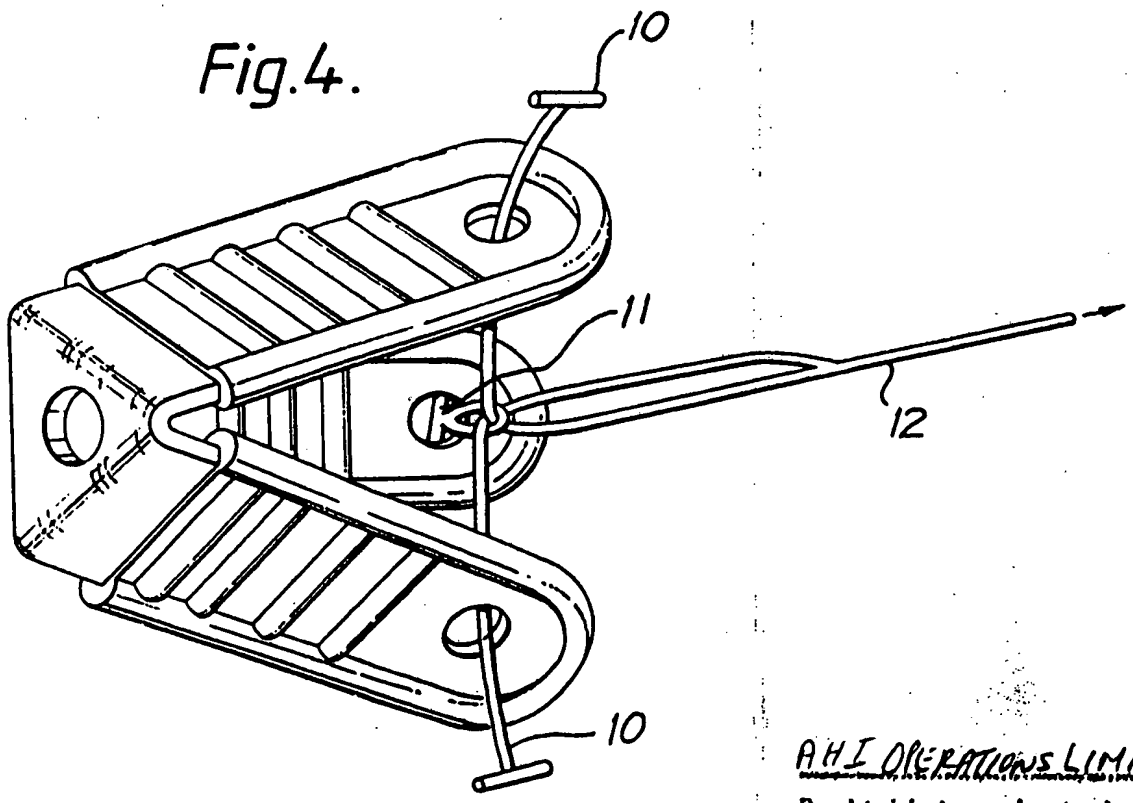


Fig.4.



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By their authorised Agents
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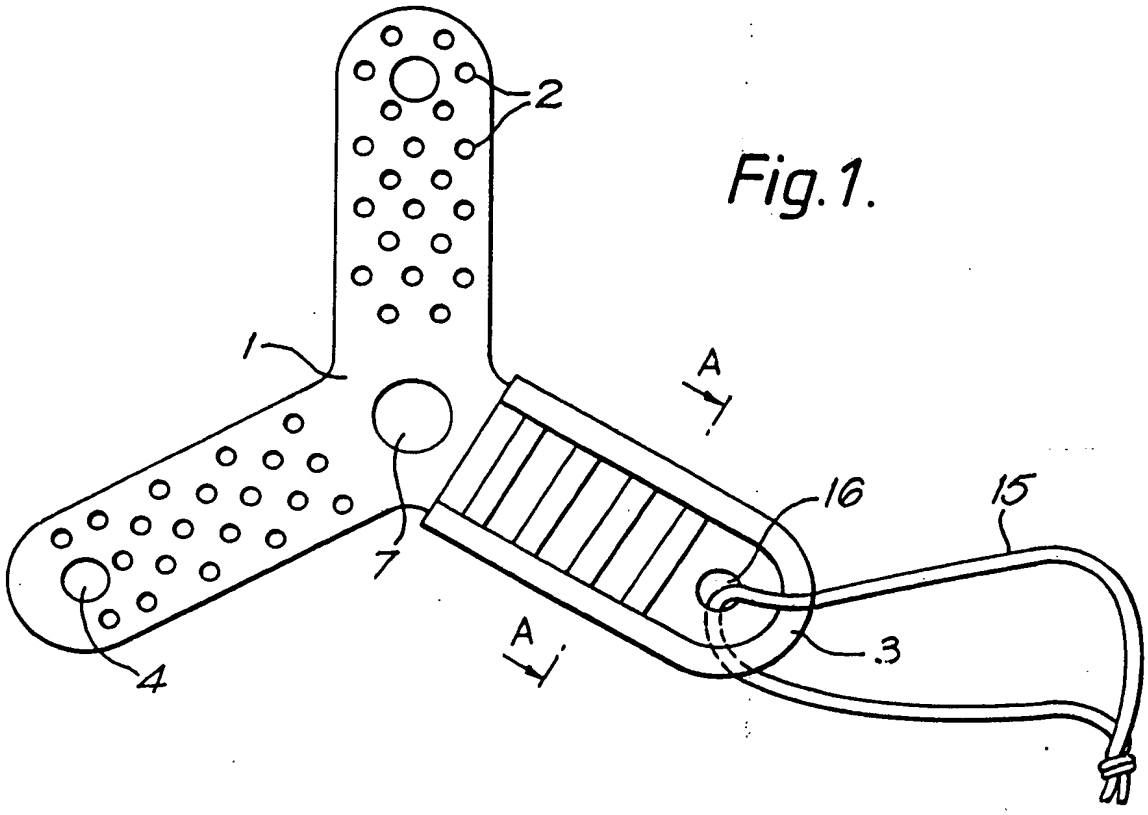
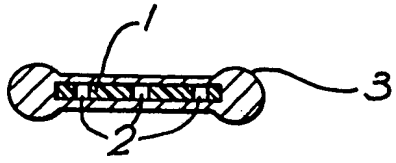


Fig.1.

Fig.2.



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